13. A pharmaceutical composition for inhibiting tumorigenicity of neoplastic cells in a human or mouse comprising an effective amount of at least one oligonucleotide as set forth in claim 6; and a pharmaceutically physiologically acceptable carrier or diluent.

14. A pharmaceutical composition for inhibiting tumorigenicity of neoplastic cells in a human or mouse comprising an effective amount of at least one oligonucleotide as set forth in claim 9; and a pharmaceutically physiologically acceptable carrier or diluent.

15. A pharmaceutical composition for inhibiting metastasis of neoplastic cells in a human or mouse comprising an effective amount of at least one oligonucleotide as set forth in claim 9, or the antisense sequence thereof; and a pharmaceutically physiologically acceptable carrier or diluent.

16. A pharmaceutical composition for inhibiting tumorigenicity of neoplastic cells in a human or mouse comprising an effective amount of at least two oligonucleotides, or analogues thereof, each comprising at least seven nucleotides having a sequence corresponding to the sequence of a 3'-UTR of a human or mouse ribonucleotide reductase R1 or R2 mRNA, wherein each oligonucleotide exhibits reduced oligonucleotide-oligonucleotide dimer formation, reduced self-complementary interactions and reduced binding potential to said R1 or R2 mRNA; and a pharmaceutically physiologically acceptable carrier or diluent.

30. The oligonucleotide as set forth in claim 1 comprising at least two sequences each corresponding to a portion of a 3'-UTR of a human or mouse ribonucleotide reductase R1 or R2 mRNA.

REMARKS

Upon entry of this Amendment, Claims 1, 6-16 and 30 will be pending. The foregoing amendments are made without any intention to abandon the subject matter of the claims as filed, but with the intention that claims of the same, lesser, or greater scope may be pursued in the present application or in a continuation, continuation-in-part, or divisional application.

These amendments add no new subject matter. Support for the amendments to Claims 1, 6-16 and 30 can be found in the Claims as originally filed.

I. Rejection of Claims Under 35 U.S.C. §112, Second Paragraph

Claims 4 and 17

The Examiner has rejected Claims 4 and 17 indicating that from the language it is not clear what structures and by what mechanism the oligonucleotides of the invention are supposed to "exhibit reduced dimer formation, reduced self-complementary interactions and reduced binding potential to the untranslated region." These claims have been cancelled without prejudice and the remaining claims have been amended to clarify that the sequences of the oligonucleotides are selected to exhibit reduced *oligonucleotide-oligonucleotide* dimer formation, self-complementary interactions and binding potential to the UTR of a ribonucleotide reductase mRNA.

Applicants have provided in the Specification, for example, at page 12, lines 17-33, page 13 at lines 22-27 and on page 54 in the footnotes for Tables 4 and 5, teaching regarding methods for determining whether an oligonucleotide of the present invention, exhibits reduced dimer formation, reduced self-complementary interactions and reduced binding potential with respect to a UTR sequence segment of the mRNA. The Examples provide a demonstration of application of these methods in the identification, preparation and characterization of exemplary oligonucleotides according to the present invention. Accordingly, one skilled in the art would readily appreciate the meaning of the phrase "wherein the oligonucleotide exhibits reduced oligonucleotide-oligonucleotide dimer formation, reduced self-complementary interactions and reduced binding potential to said mRNA". Applicants respectfully request withdrawal of the this rejection under §112, second paragraph.

Claims 6-11 and 16-17

The Examiner has rejected Claims 6-11 and 16-17 for reciting the language "substantially free" alleging that the sequence range used to define the scope of the region that is "substantially free of the coding sequence" can not be determined from such language. Applicants have cancelled claim 17 and removed the language "substantially free of the coding sequence" from

the remaining claims in question. Accordingly, Applicants believe that this objection is now rendered moot and respectfully request withdrawal of this rejection.

Claim 30

The Examiner has rejected Claim 30 indicating that the language of two sequences "linked together" is such that the structure of the claimed invention can not be envisioned. Applicants have amended Claim 30 clarifying the metes and bounds of the sequence of the oligonucleotide and deleting the phrase "linked together." Accordingly, Applicants believe this objection is now rendered moot.

On the basis of the foregoing Amendments and arguments, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 4, 6-11, 16-17 and 30, under 35 U.S.C. §112, second paragraph.

II. Rejection of Claims Under 35 U.S.C. §112, First Paragraph

The Examiner has also rejected Claims 12-17 and 31, under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification in such a way as to enable one skilled in the art to make or use the invention. Specifically, the Examiner has alleged that the specification does not "reasonably teach one skilled in the art success of reduced tumorigenicity of any neoplastic cell(s) or whole organisms [including human] via application of the 3'UTR sequences of any housekeeping gene as broadly claimed." *See,* Office Action, page 4, last paragraph.

Although the Examiner has acknowledged that it is generally known in the art that murine gene sequences can share high homology with human gene sequences, the Examiner alleges that based on the lack of general guidelines in the art for success of gene therapy applications and the lack of specific examples other than for the application of 3'UTR sequences of murine ribonucleotide reductase, the claims are not enabled for the application of 3'-UTR oligonucleotides of any housekeeping gene, in any mammal, including human. *See,* Office Action, page 6 to 7, first paragraph on that page.

Furthermore, the Examiner states that no specific examples are provided for the antisense and ribozyme sequences administered either alone or in combination with any 3'UTR housekeeping oligonucleotide. The Examiner alleges that there are several factors which act as barriers to the successful delivery of such molecules and which would therefore require undue experimentation to practice the invention without further guidance in the Specification; *i.e.* with respect to the design of stable antisense and ribozymes *in vivo*, effective delivery of same in whole organisms, dosage and toxicity, and the visualization of the desired treatment effects due to same. *See,* Office Action, pages 7, second paragraph to page 9, first paragraph.

Finally, the Examiner alleges that as the pharmaceutical compositions of the invention imply *in vivo* treatment of a patient the same factors of unpredictability relating to the use of the oligonucleotides, antisense and ribozymes of the invention, are also applicable and would require the skilled technician to undertake undue experimentation to work the invention.

Applicants traverse. "[T]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 1606 (1987). *See, also, United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343, 188 USPQ 659 (CCPA 1976); MPEP §2164.01.

Applicants respectfully disagree with the Examiner's position that the Specification is not enabled for use of the oligonucleotides, antisense and ribozymes in whole animals. The MPEP clearly indicates that human clinical data are not required. For example, MPEP §2107.02.IV states:

> **Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials.** There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974)), even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims. [Emphasis added.]

In the present Specification there is detailed disclosure on: (*i*) oligonucleotide preparation, *e.g.*, page 12, line 9 through page 15, line 16; (*ii*) how to deliver safely and achieve localization of the oligonucleotides to cells, *e.g.*, page 21, lines 30 through page 22, line 15 and page 23, line 30 through page 27, line 8; as well as how to monitor the progression of therapy using probes or antibodies that bind the UTRs, or by screening for agonists and antagonists of oligonucleotide activity, *e.g.*, page 27, line 9 through page 33, line 6. In addition, the Examiner has conceded that the Specification teaches that: (*i*) syngeneic mice injected with cancer cells transformed with vector constructs expressing the 3'UTR of murine R1 and R2, showed reduced tumors and reduced metastatic potential and (*ii*) reduced cell growth of human cancer cell lines upon transfection with whole or partial sequences of the 3'UTR of R1 and R2. *See* Office Action, page 4, paragraph beginning at line 3 through to line 15. Accordingly, Applicants respectfully remind the Examiner that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the scope of the claim, then the enablement requirement of Section 112 is satisfied." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The Examiner has alleged that the present invention has failed to provide a correlation between the expression of murine 3'UTR R1 and R2 in murine and human metastatic cells *in vitro,* and treatment effects (*i.e.*, reduced tumorigenicity, in a whole organism).

Applicants respectfully submit that the murine model is generally regarded within this field as the most appropriate model for studying anti-tumorigenic responses for testing new therapies for potential use in humans, and that the murine model is customarily used in this field to determine the potential utility of such therapies in the treatment of humans. *See, e.g.,* Paul, *et al.*, eds., 1994. *Neoplastic Disease,* pp. 128-131 (Oxford Press); Zhang, *et al.*, 1994 *Cancer Gene Ther*, 1(1): 5-13 ("Zhang"); and Wills, *et al.*, 1994 *Hum Gene Ther*, **5**: 1079-1088 ("Wills"). Zhang and Wills are directed toward the use of recombinant adenoviruses that express p53, a known tumor suppressor, in gene therapy of cancer. In both Zhang and Wills, the *in vivo* efficacy of the adenoviruses was first demonstrated using a murine model that is analogous to that used in the instant application. In particular, tumor cells were infected *ex vivo* and then injected into nude mice to "assess the ability of the recombinants to suppress tumor growth *in vivo*." (Wills, *et al.*) The results of these tests indicated that it was likely that p53 gene therapy

would be useful as a treatment of existing tumors. This was supported by the demonstration of reduced tumor growth or prevention of tumor formation results, in Wills and Zhang, respectively. These references are, therefore, indicative of the fact that the murine model used in the present application is an art recognized method of testing gene therapies and is predictive of *in vivo* efficacy.

The murine model used in the present invention has been demonstrated to be predictive of the usefulness of gene therapies in humans, as shown, for example, by Swisher, *et al.*, 1999 *J. Natl Cancer Inst*, **93**(9): 763-771; Schuler, *et al.*, 1998 *Hum Gene Ther*, **9**: 2075-2082; and Roth, *et al.*, 1996 *Nature Med*, **2**(9): 985-991. These articles summarize the results of clinical trials initiated based on the results of preclinical studies, including those described in Zhang and Wills, which made use of this model as one of the preclinical validation tests (see above). As predicted by the results from the murine model tests, the administration of gene therapy vectors that express p53 were found to be therapeutically beneficial to many of the cancer patients tested. Applicants, therefore, submit that the murine model used in the present application is an art recognized model that is predictive of clinical utility.

Furthermore, the majority of known therapeutic antisense oligonucleotides are administered without additional carrier or delivery molecules. (*See* Vitravene™ product monograph, and clinical trial protocols for G3139) For the purposes of this response Applicant is considering the testing of antisense therapeutics to be analogous to testing of gene therapy applications, in particular in terms of appropriate animal models. Applicants, therefore, assert that a worker skilled in the art, given the present Specification, could make and use the antisense oligonucleotides without undue experimentation. A publication by Agrawal and Zhao (*Curr. Opin. Chem. Biol.* 1998, **2**:519-528; "*Agrawal*") provides a review of antisense therapeutics including a discussion of promising *in vitro* results that lead to clinical trials using the antisense oligonucleotides. Although, *Agrawal* provides a discussion of "Factors affecting the antisense activities" and means of possibly improving therapeutic efficacy of antisense oligonucleotides *in vivo*, there is no suggestion that once an antisense activity is found using *in vitro* techniques that it would not be expected to act similarly *in vivo*. In fact *Agrawal* teaches that the opposite is true.

Furthermore, as the Examiner has conceded that "it is generally known in the art that murine gene sequences can share high homology with human gene sequences...." it would be apparent to one of ordinary skill in the relevant art that the successful *in vitro* human and *in vivo* murine experiments disclosed in the present application show that the compositions of the present invention would have a therapeutic effect when administered to a human patient (*i.e.*, that there would be a reasonable correlation between the *in vitro* and *in vivo* data and therapeutic effectiveness in humans).

As the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating. *See, Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, first paragraph -- Enablement Chemical/Biotechnical Applications.* "Based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).

The evidence provided by Applicant need not be *conclusive* but merely *convincing* to one skilled in the art. *Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, first paragraph -- Enablement Chemical/Biotechnical Applications.* Thus, the Applicants, absent some *definitive* scientific basis to conclude that *in vivo* animal models do not correlate with other mammals in this instance, should be allowed to maintain the scope of their claims to all mammals, including humans, without providing clinical efficacy.

With respect to the requirement for human testing, the MPEP expressly states that human clinical data is *not* required for enablement under 35 U.S.C §112, first paragraph. For example, the MPEP states:

> **Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials.** There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (*see, In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA

> 1974)), even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims.

MPEP §2107.02.IV [emphasis added].

Additionally, the MPEP indicates that data from *in vitro* assays **or** testing in an animal model is generally sufficient:

> If reasonably correlated to the particular therapeutic or pharmacological utility, **data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient** to establish therapeutic or pharmacological utility for a compound, composition or process.

MPEP §2107.02.III [emphasis added.].

The MPEP further states that:

> **The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted.** Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980).

MPEP §2107.02.I [emphasis added.].

Regarding the Examiner's allegation that "undue experimentation" would be required by one skilled in the art to practice the present invention, Applicant respectfully reminds the Examiner that the amount of experimentation that is permissible to provide enablement depends upon a number of factors, which include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the breadth of the claims. *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988); MPEP §2164.01.

It is well established in patent law that a requirement of experimentation by a skilled person does not preclude enablement; all that is required is that the amount of experimentation not be *unduly extensive*. Additionally, "[t]he fact that experimentation may be complex. . . does not necessarily make it undue, if the art typically engages in such experimentation." *Massachusetts Institute of Technology v. AV Frotia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (*citing, In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). Similarly, "[t]ime and difficulty of experiments are not determinative if they are merely routine." *United States v. Telectonics Inc.,* 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

As previously discussed the present invention provides a great deal of support for the production, screening, and therapeutic use of the oligonucleotides disclosed herein. Any additional experimentation which may be subsequently required in the practice of the invention would merely entail following the methods disclosed within the Specification which comprise *conventional* assays and guidelines *known* within the art. This type of well-supported, well-known, and clearly delineated experimentation is allowed under 35 U.S.C §112, first paragraph. For example, claims directed to a "biologically-active" compound were held to be enabled if, at the time of filing, it would have been routine for the skilled artisan to identify such a compound using conventional screening assays. *See, Ex parte Mark*, 12 USPQ2d 1904 (BPAI).

In order, however, to expedite examination, Applicants have cancelled Claim 31 and amended Claims 12-17 to refer to oligonucleotides of a 3'UTR of a human or mouse ribonucleotide reductase gene to inhibit tumorigenicity in a human or mouse. Claim 31 has been cancelled with prejudice or disclaimer.

Applicants request the right to pursue the withdrawn subject matter in a subsequent continuation, continuation-in-part or divisional application and respectfully request that the Examiner reconsider and withdraw the rejection of Claims 12-17 under 35 U.S.C. §112, first paragraph. Claim 31 has been cancelled with prejudice or disclaimer.

II. Rejection of Claims Under 35 U.S.C. §102(b)

The standard of anticipation under 35 U.S.C. §102(b) is that each and every element of the claim must be found in the cited reference. *In re Marshall* (CCPA 1978), 198 USPQ 344.

Pavlov et al.

The Examiner has rejected Claims 1-7 and 9-10 under 35 U.S.C. §102(b) as being anticipated by Pavlov et al. This rejection is traversed in part and obviated in part for the following reasons.

Pavlov et al. teach the full length gene sequences of the human R1 and R2 ribonucleotide reductase including the 3' UTR sequences. Pavlov et al. do not teach oligonucleotides with sequences corresponding to said 3'UTR sequences which show reduced *oligonucleotide-oligonucleotide* dimer formation, reduced self-complementary interactions and reduced *oligonucleotide* binding potential to said 3'UTR of a ribonucleotide reductase gene and which inhibit tumor cell growth.

Claim 1, as amended, is directed to an oligonucleotide comprising at least seven consecutive nucleotides of a 3'UTR region of a ribonucleotide reductase gene characterized in that the oligonucleotide shows reduced *oligonucleotide-oligonucleotide* dimer formation, reduced self-complementary interactions and reduced *oligonucleotide* binding potential to said 3'UTR of a ribonucleotide reductase mRNA and which inhibits tumor cell growth. Claim 6 depends from Claim1 and Claim 7 from Claim 9. Claim 9 also depends from Claim 1 and Claim 10 from Claim 9. Claims 2-5 have been cancelled without prejudice and disclaimer.

Accordingly, as Pavlov et al. does not teach every element of the claimed invention the requirement under 35 U.S.C. §102(b) is not satisfied. Applicants respectfully request the withdrawal of this rejection.

Amara et al.

Claims 1-3 and 5 stand rejected under 35 U.S.C. §102(b) as being anticipated by Amara et al. The rejection is traversed-in-part and obviated-in-part as set forth below.

Amara et al. teach the sequence of a 9-nucleotide cis element in the 3'-UTR of mouse ribonucleotide reductase. This reference does not teach oligonucleotides which show reduced *oligonucleotide-oligonucleotide* dimer formation, reduced self-complementary interactions and reduced *oligonucleotide* binding potential to said 3'UTR of a ribonucleotide reductase mRNA and which inhibit tumor cell growth.

Claim 1, as amended, is directed to an oligonucleotide comprising at least seven nucleotides corresponding to a 3'UTR sequence of a ribonucleotide reductase gene and which shows reduced *oligonucleotide-oligonucleotide* dimer formation, reduced self-complementary interactions and reduced *oligonucleotide* binding potential to said 3'UTR of a ribonucleotide reductase gene and which inhibits tumor cell growth. Therefore, Amara et al. does not teach each and every element recited in the claims and accordingly, Applicants respectfully request withdrawal of this rejection withdrawn.

Voss et al.

Claims 1 stands rejected under 35 U.S.C. §102(b) as being anticipated by Voss et al. The rejection is obviated as set forth below.

Voss et al. teach the sequence of human casein kinase II subunit beta. Voss et al. do not teach the sequence of the ribonucleotide reductase gene.

Claim 1, as amended, is directed to an oligonucleotide comprising at least seven consecutive nucleotides of an untranslated region of a ribonucleotide reductase gene characterized in that the oligonucleotide has increased stability in the presence of a nuclease and is capable of inhibiting tumor cell growth.

Therefore, Voss et al. does not teach each and every element recited in the claims. Accordingly, Applicants respectfully request withdrawal this rejection.

Hilfiker et al.

Claim 1 stands rejected under 35 U.S.C. §102(b) as being anticipated by Hilfiker et al. The rejection is obviated as set forth below.

Hilfikèr et al. teaches the sequence of human plasma membrane calcium pump isoform 1. Hilfiker et al. does not teach the sequence of the ribonucleotide reductase gene.

Claim 1, as amended, is directed to an oligonucleotide comprising at least seven consecutive nucleotides or nucleotide analogues of an untranslated region of a ribonucleotide reductase gene characterized in that the oligonucleotide has increased stability in the presence of a nuclease and is capable of inhibiting tumor cell growth.

Therefore, Hilfiker et al. does not teach each and every element recited in the claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Finally, Applicants reiterate that the foregoing amendments are made without any intention to abandon the subject matter of the claims as filed, but with the intention that claims of the same, lesser, or greater scope may be pursued in the present application or in a continuation, continuation-in-part, or divisional application. In particular, Applicant asserts that oligonucleotides to the 3'UTR of other housekeeping genes, or the antisense thereof, or ribozymes complementary or homologous to said oligonucleotides are properly within the scope of the invention, for example, see page 5, lines 4 to 9 of the Specification. In order to expedite examination of the instant application, however, Applicant has limited the claims to oligonucleotides of the 3'UTR of human or mouse ribonucleotide reductase genes.

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b).

CONCLUSION

On the basis of the foregoing claim amendments and remarks, Applicants respectfully submit that, upon entry, the new pending claims will be in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Dated: March 20, 2001

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Version With Markings to Show Changes

Claims 2-5, 17 and 31 were canceled.

Claims, 1, 6-16 and 30 have been amended as follows:

1. (Amended) An [synthetic] oligonucleotide, or analogue thereof, which inhibits neoplastic cell growth, comprising at least seven nucleotides [or nucleotide analogues] having a sequence corresponding to the sequence of a 3'-UTR [entire untranslated 3' region (3'-UTR)] of a human or mouse ribonucleotide reductase R1 or R2 mRNA, [of mRNA of a housekeeping gene or a consecutive sequence segment of said 3'UTR], wherein the oligonucleotide exhibits reduced oligonucleotide-oligonucleotide dimer formation, reduced self-complementary interactions and reduced binding potential to said mRNA.

6. (Amended) The [synthetic] oligonucleotide, or analogue thereof, as set forth in claim 1 [5] wherein the oligonucleotide comprises [has] a sequence corresponding to the [entire] sequence of the 3'-UTR of a human or mouse ribonucleotide reductase R1 mRNA [for the R1 component] as set forth in SEQ ID No: 1 [(SEQ ID No:1) of or segment thereof substantially free of the coding sequence of ribonucleotide reductase protein R1].

7. (Amended) The [synthetic] oligonucleotide, or analogue thereof, as set forth in claim 6 wherein the oligonucleotide comprises [segment has] a sequence as set forth in SEQ ID Nos: 44, 45, 46, 47, 48, or 49 [Table 4].

8. (Amended) The [synthetic] oligonucleotide, or analogue thereof, as set forth in claim 6 wherein the oligonucleotide comprises [segment has] a sequence as set forth in SEQ ID No: 45.

9. (Amended) The [synthetic] oligonucleotide, or analogue thereof, as set forth in claim 1 [5] wherein the oligonucleotide comprises [has] a sequence corresponding to the [entire] sequence of the 3'-UTR of a human or mouse ribonucleotide reductase R2 mRNA [for the R2 component] as set forth in SEQ ID No: 2 [(SEQ ID No:2) of or segment thereof substantially free of the coding sequence of ribonucleotide reductase protein R2].

10. (Amended) The [synthetic] oligonucleotide, or analogue thereof, as set forth in claim 9 wherein the oligonucleotide comprises [segment has] a sequence as set forth in SEQ ID Nos: 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, or 43 [Table 5].

11. (Amended) The [synthetic] oligonucleotide, or analogue thereof, as set forth in claim 9 wherein the oligonucleotide comprises [segment has] a sequence as set forth in SEQ ID Nos: 6, 7, 8, 9, 10, 11, or [-]12.

12. (Amended) A pharmaceutical composition for inhibiting [the] tumorigenicity of neoplastic cells in a human or mouse comprising [mammal consisting of] an effective amount of at least one oligonucleotide [active ingredient] as set forth in claim 1; and a pharmaceutically physiologically acceptable carrier or diluent.

13. (Amended) A pharmaceutical composition for inhibiting [modulating] tumorigenicity of neoplastic cells in a human or mouse comprising [mammal consisting of] an effective amount of at least one oligonucleotide [active ingredient] as set forth in claim 6[, or the antisense sequence thereof, or a ribozyme comprising a sequence complementary to at least a portion of said UTR]; and a pharmaceutically physiologically acceptable carrier or diluent.

14. (Amended) A pharmaceutical composition for inhibiting [modulating] tumorigenicity of neoplastic cells in a human or mouse comprising [mammal consisting of] an effective amount of at least one oligonucleotide [active ingredient] as set forth in claim 9[, or the antisense sequence thereof, or a ribozyme comprising a sequence complementary to at least a portion of said UTR]; and a pharmaceutically physiologically acceptable carrier or diluent.

15. (Amended) A pharmaceutical composition for inhibiting metastasis of [a] neoplastic cells in a human or mouse comprising [mammal consisting of] an effective amount of at least one oligonucleotide [active ingredient] as set forth in claim 9, or the antisense sequence thereof, [or a ribozyme comprising a sequence complementary to at least a

portion of said UTR]; and a pharmaceutically physiologically acceptable carrier or diluent.

16. (Amended) A pharmaceutical composition for inhibiting [modulating] tumorigenicity of [a] neoplastic cells in a human or mouse comprising [mammal consisting of] an effective amount of at least two [active ingredients selected from] oligonucleotides, or analogues thereof, each comprising at least seven nucleotides having a sequence corresponding to the [entire] sequence of a 3'-UTR of a human or mouse ribonucleotide reductase R1 or R2 [the] mRNA, [for the R1 or R2 component or sequence segments of at least seven consecutive nucleotides thereof substantially free of the coding sequence of ribonucleotide reductase protein R1 or R2 respectively or the antisense sequences thereof or ribozymes comprising a sequence complementary to at least a portion of said UTR] wherein each oligonucleotide exhibits reduced oligonucleotide-oligonucleotide dimer formation, reduced self-complementary interactions and reduced binding potential to said R1 or R2 mRNA; and a pharmaceutically physiologically acceptable carrier or diluent.

30. (Amended) The [A synthetic] oligonucleotide as set forth in claim 1 comprising at least two sequences [of a consecutive segment] each corresponding to a portion of a 3'-UTR of a human or mouse ribonucleotide reductase R1 or R2 mRNA [an untranslated 3' region (3'-UTR) of mRNA of a housekeeping gene linked together].